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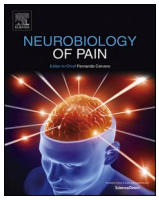

Exercise therapy for chronic pain: How does exercise change the limbic brain function?

Emiko Senba [a,c,*], Katsuya Kami [b,c]

[a] Department of Physical Therapy, Osaka Yukioka College of Health Science, 1-1-41 Sojiji, Ibaraki-City, Osaka 567-0801, Japan
[b] Department of Rehabilitation, Wakayama Faculty of Health Care Sciences, Takarazuka University of Medical and Health Care, 2252 Nakanoshima, Wakayama City, Wakayama 640-8392, Japan
[c] Department of Rehabilitation Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama City, Wakayama 641-8509, Japan

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ABSTRACT

We are exposed to various external and internal threats which might hurt us. The role of taking flexible and appropriate actions against threats is played by "the limbic system" and at the heart of it there is the ventral tegmental area and nucleus accumbens (brain reward system). Pain-related fear causes excessive excitation of amygdala, which in turn causes the suppression of medial prefrontal cortex, leading to chronification of pain.

Since the limbic system of chronic pain patients is functionally impaired, they are maladaptive to their situations, unable to take goal-directed behavior and are easily caught by fear-avoidance thinking.

We describe the neural mechanisms how exercise activates the brain reward system and enables chronic pain patients to take goal-directed behavior and overcome fear-avoidance thinking. A key to getting out from chronic pain state is to take advantage of the behavioral switching function of the basal nucleus of amygdala. We show that exercise activates positive neurons in this nucleus which project to the nucleus accumbens and promote reward behavior.

We also describe fear conditioning and extinction are affected by exercise. In chronic pain patients, the fear response to pain is enhanced and the extinction of fear memories is impaired, so it is difficult to get out of "fear-avoidance thinking". Prolonged avoidance of movement and physical inactivity exacerbate pain and have detrimental effects on the musculoskeletal and cardiovascular systems.

Based on the recent findings on multiple bran networks, we propose a well-balanced exercise prescription considering the adherence and pacing of exercise practice. We conclude that therapies targeting the mesocortico-limbic system, such as exercise therapy and cognitive behavioral therapy, may become promising tools in the fight against chronic pain.

Introduction

In developed countries, about 15–20% of the population suffers from chronic pain (Dahlhamer et al., 2016; Yong et al., 2022), which means not only a disruption of patients' healthy lives, but also a socioeconomic burden. Prevalence is consistently higher in women and elderly people (Fayaz et al., 2016). Elucidating the mechanism by which pain becomes chronic is an urgent task from the viewpoint of prevention and treatment. The restructuring of synaptic plasticity and neural networks at various levels of the nervous system sustains chronic pain even when there are no longer peripheral pain stimuli (pain centralization). The development of brain imaging to clarify the structure, function, and networks of the brain has led to a rapid understanding of the role of the brain in the chronification of pain (Schmidt-Wilcke, 2015). Chronic refractory pain includes neuropathic pain (NPP), complex regional pain syndrome (CRPS), postherpetic neuralgia, etc., in which we can identify the disease or injury that triggers the onset of pain, and nociplastic pain (Kosek et al., 2021), which does not show any structural abnormalities that cause pain and may include fibromyalgia (FM), temporomandibular disorder (TMD), chronic low back pain (CBP), irritable bowel syndrome (IBS) etc.

At present, there is no medicine that works for such chronic pain states. For example, gabapentinoid, tricyclic antidepressant, SNRI are designated as first-line drugs for neuropathic pain. Nevertheless, the

* Corresponding author at: Department of Physical Therapy, Osaka Yukioka College of Health Science, 1-1-41 Sojiji, Ibaraki-City, Osaka 567-0801, Japan.
E-mail address: emiko-senba@yukioka-u.ac.jp (E. Senba).

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NPT (number needed to treat) is rather high. Because they do not work well, many patients suffer from side effects by increasing the dose of the drug or taking it for a long time. It is still fresh in our memories that uncontrolled opioid use for chronic pain patients has caused a disaster in North America. In such a situation, non-pharmacological treatments, such as exercise therapy and cognitive behavioral therapy (CBT) have attracted attention as a safe and effective treatment for chronic pain without side effects and are strongly recommended in the guidelines for the treatment of chronic pain in many countries.

Patients with chronic pain have stress or anxiety. Chronic pain is stressful, and long-lasting pain causes psychosocial problems and lowers the QOL of sufferers. In particular, chronic pain, depression, and sleep disorders are all easily complicated symptoms, and are called Triads (Senba, 2015). The psychosocial factors of each patient act as stressors to further aggravate the symptoms, such as cognitive deficits, hypervigilance, emotional changes, memory deficits, and decreased motivation (Simons et al., 2014).

Now we are aware that brain systems working in acute pain and chronic pain are quite different. The former uses traditional pain transmission system, while the limbic system plays a crucial role in the latter (Simons et al., 2014). It has been demonstrated that brain activity for back pain in the early, acute/subacute back pain group is limited to regions involved in acute pain, whereas in the chronic back pain group, activity expands to emotion-related circuitry of the limbic system (Apkarian et al., 2013; Hashmi et al., 2013; Vachon-Presseau et al., 2016a; Baria et al., 2016).

It is interesting and suggestive that persistent inflammatory pain in rats activates the network which is dependent on the activity of the right amygdala (Amyg), including bilateral infralimbic cortex (IL), bilateral nucleus accumbens (NAc), bilateral caudate putamen (CP), right globus pallidus (GP), bilateral ventral tegmental area (VTA), and bilateral substantia nigra (SN), in addition to the so-called pain transmission areas (Arimura et al., 2019). Persistent pain is somewhere between acute/experimental pain and chronic pain. So, activation of limbic system, reward system and basal ganglia may indicate the transition of activated brain areas accompanying the pain chronification.

To confront and overcome chronic pain, we must know the function and role of the limbic system. The ability to determine the surrounding situation, changes in the environment, and whether to avoid or get close to them through sensory input, and to link them to action is extremely important for the survival of living organisms, including humans. It is the “limbic system” that plays such a role, and its work constitutes a large part of our brain function. Whether you run away in fear or approach a reward, this mode of judgment and behavior is an essential ability for all living things, including humans, to survive, and has been acquired and developed over the course of a long evolutionary process. In fear conditioning, when a cue such as a sound stimulus is given along with an electric shock, it will show a fear response to the cue, in which case the Amyg is playing a central role. In addition, when an animal shows a fear response due to memory of the situation or place to which he/she has been given an electric shock, not only the Amyg but also the hippocampus (HPC) is required (Izquierdo et al., 2016).

The decision or motivation to flee or get close is transmitted to the nucleus accumbens (NAc), which is the interface between the limbic and motor systems (Mogenson et al., 1980). But you can’t react to all the incoming information. Therefore, the prefrontal cortex was developed to properly control the Amyg. In particular, the medial prefrontal cortex (mPFC) communicates cognition-based decisions to the NAc, and we can cope with the environment. In addition to the brain reward system, i.e., projection from the ventral tegmental area (VTA) to the NAc, the limbic system includes the Amyg, mPFC, and HPC, therefore it is also called the mesocortico-limbic system. Limbic regions are now expanding to include a part of basal ganglia and hypothalamus. Limbic brain science has been advancing at a remarkable pace in recent years, and this review introduces the latest findings and considers the relationship with pain and pain behavior.

In this review, we will first describe the characteristics of brain function in patients with such chronic pain and explain how they change with the implementation of exercise. Furthermore, we approach this problem from three aspects of the brain function: (i) the limbic system, (ii) fear conditioning, and (iii) brain networks. The limbic system allows us to act appropriately in the situation we are in. Since the fear-avoidance thinking plays an important role in pain chronification, breaking out from that thinking is very important for the treatment of chronic pain (Kami et al., 2022). It is also essential to understand that the brain does not work separately but by forming multiple brain networks. We consider that understanding these three dimensions of brain function is essential for the development of effective exercise therapy prescriptions for chronic pain.

The limbic system is dysfunctional in chronic pain state

It is well known that the chronification of pain involves a dysfunction of the mesocortico-limbic system, including the brain reward system. The activity of the NAc is reduced in chronic pain patients by the following two mechanisms. One is (1) in chronic pain conditions glutamate (Glu) neurons in the lateral habenular nucleus (LHb) are activated by the direction of globus pallidus (GP) and γ-aminobutyric acid (GABA) neurons in the rostromedial tegmental nucleus (RMTg) are activated, which then suppress DA neurons in the latVTA (Jhou et al., 2009) and reduce DA-ergic input to the NAc lateral shell. The GP neurons projecting to the LHb (GPh) are located in the border region of the GP (GPb) in primates (Hong and Hikosaka, 2013), which corresponds to the entopeduncular nucleus (EPN) in rodents (Li et al., 2019). This involves a **GPh(EPN)-LHb-RMTg-latVTA-NAc system.** The second is (2) Glu neurons in the basolateral nucleus of amygdala (BLA) that are overexcited by persistent pain and pain-related fear, project to the mPFC and activate GABA interneurons that in turn inhibit Glu neurons in the mPFC projecting to the NAc (Ji et al., 2010; Ji and Neugebauer, 2011). This involves an **BLA-mPFC-NAc system.** Then activity of the NAc GABA neurons is reduced through these two feed-forward inhibitions via activation of GABA neurons. **Parabrachial nucleus (PBN)-SN pars reticulata-VTA** system may also contribute to the deactivation of VTA DA neurons (Yang et al., 2021).

In patients with chronic low back pain, reward network dysfunction and dopaminergic dysregulation have been observed (Yu et al., 2020), and NAc activation does not occur at the time of relief from pain stimuli compared to healthy patients (Baliki et al., 2010). In patients who have subacute low back pain that becomes chronic low back pain after 1 year, high functional connectivity between the PFC and NAc was observed from the first consultation (Baliki et al., 2012). Furthermore, in a group of patients who had persistent low back pain for 3 years, it was found that the white matter connections between the dorsomedial PFC (dmPFC)-Amyg-NAc were strong from the first consultation (Vachon-Presseau et al., 2016b). Since high functional or white matter connectivity means that these areas work synchronously, those patients tend to be susceptible to the effects of fear of pain and their pain may be more likely to become chronic. The mPFC is an area related to anxiety and emotions associated with pain (Ong et al., 2019), and dmPFC (prelimbic cortex in rodents) is involved in fear conditioning (Sierra-Mercado et al. 2011). The strong functional connectivity of dmPFC-Amyg-NAc means that they cannot move their bodies (=immobility) due to fear of causing pain, and therefore they easily fall into a “fear-avoidance thinking” by which pain is enhanced and chronified. If you as a medical staff grasp the characteristics of patients’ brain that are prone to transition to chronic pain at the time of the first visit, and apply interventions, such as exercise therapy and/or CBT from an early stage, there is a possibility that the transition to chronic pain can be prevented.

Structure and function of the mesocortico-limbic system

An overview of the mesocortico-limbic system

The limbic system is driven by two powerful motors, "emotion" and "reward", to produce "action". Fig. 1 summarizes the structure and functions of the limbic system. The NAc is the linchpin of the limbic system and acts as the interface connecting the limbic and motor systems by which "motivation" gets translated into "action" (Mogenson et al., 1980; Grace et al., 2007; Floresco, 2015). NAc receives glutamatergic (Glu-ergic) projections from the BLA, mPFC, and ventral hippocampus (vHPC). Based on emotional, cognitive, and experiential information, NAc determines the direction of action and inform it onto the ventral pallidum (VP) (Grace et al., 2007). The VP, through the thalamic dorsal medial nucleus (TMD), gives feedback to mPFC, and LHb also get feedback from the VP. Then LHb makes a judgment and modify the action through the reward system.

The VP is a critical node in the mesolimbic network, being the primary output of the NAc and projecting to the LHb and VTA (Wulff et al., 2019). The VP plays a crucial role in the processing and execution of motivated behaviors (Root et al., 2018). The VP has reciprocal connections with the mPFC, Amyg, LH, VTA, PBN, subthalamic nucleus and other reward-related structures. It has direct projections to mPFC, and dense projections to TMD, which relays in turn to mPFC. It should be emphasized that the VP mediates reward and motivation functions at many levels in the brain, in addition to aiding translation to movement (Smith et al., 2009; Wulff et al., 2019). Although most of VP neurons are GABA-ergic, substantial proportion of them are Glu-ergic (Hur and Záborszky, 2005). These Glu-ergic VP neurons increase activity of the LHb, RMTg, and GABA-ergic VTA neurons (Tooley et al., 2018), leading to inhibition of VTA DA neurons. Selective activation of Glu-ergic VP neurons induced a place avoidance (Tooley et al., 2018). GABAergic VP neurons are essential for movements toward reward, while Glu-ergic VP neurons work for movements to avoid a threat (Stephenson-Jones et al., 2020).

The LHb also has rich afferent and efferent interconnections and has been regarded as a linchpin of 'limbic' and 'pallidal' parts of the brain, which enables adaptive behaviors to environment (Zahm and Root, 2017). The LHb is a phylogenetically well conserved ancient brain structure identified in virtually all vertebrate species (Freudenmacher, et al.,2020; Hu et al., 2020). How good or how bad judgment of the surrounding situation is carried out by the GPe-GPi border region (GPb) in primate, and in the worst case GPb neurons excites LHb (Hong and Hikosaka, 2008, 2013). These GPb neurons projecting to LHb (GPh) are excited by the no-reward predicting cues, such as stress and pain, and inhibited by the reward-predicting cues (Hong and Hikosaka, 2008; Li et al., 2019). In rodents the EPN is homologous to the GPi in primates and human (Li et al., 2019). Chronic pain/stress activates **EPN → LHb → VTA** pathway (Cerniauskas et al., 2019). The LHb receives excitatory inputs from a wide range of limbic structures including the EPN, lateral hypothalamic area (LHA), bed nucleus of stria terminalis (BNST) and medVTA (Nuno-Perez et al., 2021). Although the output of the basal ganglia is primarily inhibitory, GPi inputs to the LHb is excitatory and Glu-ergic (Shabel et al., 2014). These GPh neurons are phasically excited by punishment-predictive tones (Stephenson-Jones et al., 2016). LHb receives co-transmitted Glu and GABA from VTA and EPN. In these terminals, Glu and GABA are distributed in separate synaptic vesicles (Root et al., 2018). These Glu-GABA co-transmitting neurons in the VTA preferentially project to the LHb (Root et al., 2018).

Ventral tegmental area (VTA)-

The brain reward system is a system in which VTA DA neurons project onto the NAc to act on GABA-ergic medium spiny neurons (MSNs) in the NAc. Since injection of apomorphine (D2/D1 agonist) into the NAc causes analgesia (Sarkis et al., 2011), DA input to NAc is

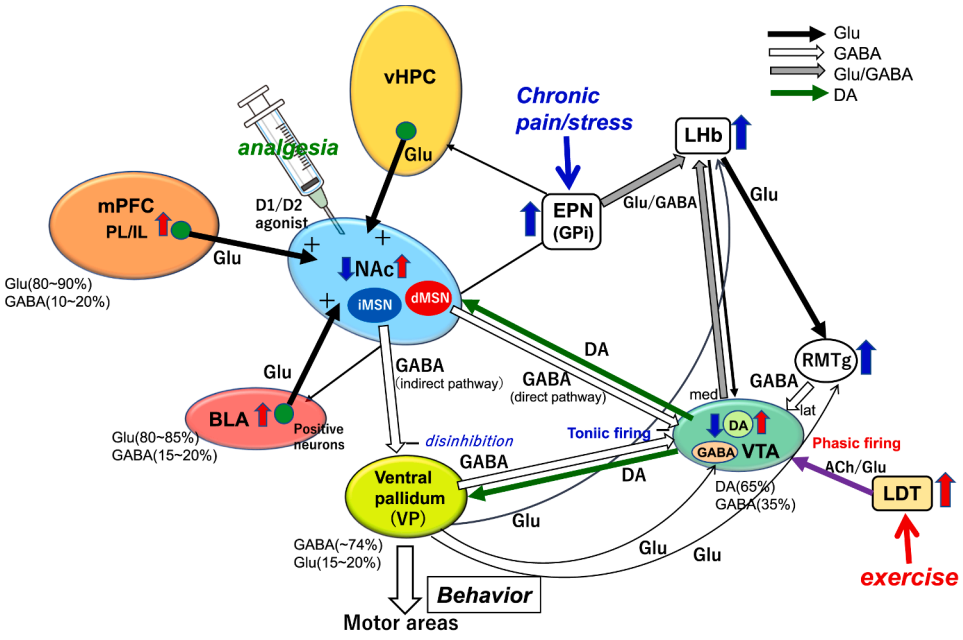

Fig. 1. Structure and function of the mesocortico-limbic system The phasic/tonic activities of the VTA DA neurons are maintained by inputs from LDT and VP, respectively. NAc receives information about various aspects of environment and emotion from mPFC, Amyg, and ventral hippocampus(vHPC). DA neurons project to the NAc to control medium spiny neurons (MSNs). DA excites the direct pathway MSN (dMSN) of the NAc and suppresses the indirect pathway MSN (iMSN). iMSN controls the motor system through disinhibition of VP, and VP neurons cause tonic firing of VTA DA neurons by disinhibition. LHb receives information from the EPN (GPi in human) of the basal ganglia. In chronic pain state, excitation of EPN-LHb pathway excites RMTg GABA neurons, which inhibit VTA DA neurons (blue arrows). Conversely, exercise activates these nuclei in the limbic system (red arrows). Injection of DA agonist into the NAc works on analgesia. DA excites dMSN expressing D1-R and inhibits iMSN expressing D2-R (Grace et al, 2007). Excitation of iMSN inhibits VP GABA neurons, causing tonic firing of DA neuron in the VTA by disinhibition. Abbreviations: ACh, acetylcholine; BLA, basolateral nucleus of amygdala; DA, dopamine; dMSN, direct pathway MSN; EPN, entopedunclar nucleus; GABA, γ-aminobutyric acid; Glu, glutamate; GPi, internal segment of globus pallidus; iMSN, indirect pathway MSN; IL, infralimbic cortex; LDT, laterodorsal tegmental nucleus; LHb, lateral habenular nucleus; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; NAc, nucleus accumbens; PL, prelimbic cortex; RMTg, rostromedial tegmental nucleus; vHPC, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

thought to act as analgesic (Fig. 1).

Until now, the role of DA has been discussed based on the reward prediction error (RPE) hypothesis (Schulz, 2016). However, not all DA neurons strictly follow this RPE model. Increased DA release in response to aversive events, such as acute stress or pain produced by injection of hypertonic saline, has been reported (Wood, 2004; Wood et al., 2007). On the other hand, fibromyalgia patients showed disrupted dopaminergic reactivity in response to acute pain (Wood et al., 2007).

VTA dopamine-releasing neurons are heterogeneous in their afferent and efferent connectivity and, in some cases, release GABA or glutamate in addition to dopamine (Morales and Margolis, 2017; Verharen et al., 2020). About 65% of VTA neurons are DA-ergic and 35% are GABA-ergic, although different DA/GABA ratios were seen among the different subnuclei of VTA. Only 2–3% of total VTA neurons are glutamatergic (Nair-Roberts et al., 2008; Bouarab et al., 2019).

The main sources of input to the VTA are the LHb and the laterodorsal tegmental nucleus (LDT) of the brainstem. The latter causes phasic activity of VTA DA neurons LHb receives GPi (EPN) inputs (co-release of Glu and GABA) (Root et al., 2018) that are activated by aversive stimuli such as chronic pain and chronic stress. LHb then sends Glu-ergic projections to DA neurons of medVTA, while RMTg, which receives LHb inputs, inhibits DA neurons of latVTA via its GABA-ergic input (Grace et al., 2007; Jhou et al., 2009) (Figs. 1, 2). That is, the LHb-medVTA-NAc's medial shell pathway is associated with aversion and LDT-latVTA-NAc's lateral shell pathway is involved in preference/reward behavior (Lammel et al., 2008, Lammel et al., 2012, Lammel et al., 2014). Thus, medial, and lateral VTA DA neurons have totally different functions (Fig. 2).

The nucleus accumbens (NAc)

The NAc, which is also called the ventral striatum, is divided into a core in the center and a shell around it, with different input and projection regions, suggesting that they contribute differentially to goal-directed behaviors (Baliki et al., 2013, Floresco, 2015).

NAc consists of 90–95% GABAergic medium spiny neurons (MSNs) (projection neurons), the rest are ACh-ergic and GABA-ergic interneurons. MSNs express AMPA/NMDA glutamate (Glu) receptors and receive Glu-ergic projections from the mPFC, BLA, and the vHPC, in addition to DA-nergic inputs from the VTA (Grace et al, 2007) (Fig. 1). The output system from the NAc is divided into direct and indirect pathways, and the direct pathway MSN (dMSN) has D1-R and coexists with dynorphin and projects directly into the VTA. The indirect pathway MSN (iMSN) expresses D2-R, coexists with enkephalin, and project to the VP or indirectly to the VTA via the VP (Fig. 1).

Selective stimulation of dMSN or iMSN by means of optogenetic technique resulted in sustained reward behavior and transient escape behavior, respectively (Kravitz et al., 2012). Recently, it was demonstrated that both selective activation of dMSN and selective suppression of iMSN in the NAc led to a significant relief of neuropathic pain (NPP) (Sato et al., 2022). In NPP model animals, iMSNs were selectively upregulated in the NAc (Ren et al., 2016). Moreover, injury-induced tactile allodynia was reversed by inhibiting and exacerbated by exciting iMSNs. These changes were overcome by supplementing dopamine levels with L-DOPA in combination with a D2/D3 receptor agonist, implicating that DA can be applied for the treatment of chronic pain (Ren et al., 2016). Moreover, precise reciprocal projections between the dMSNs and iMSN in the NAc and VTA neurons were reported (Yang et al., 2018). Heterogenous reactions of DA terminals in NAc subregions to aversive and reward predicting cues have been demonstrated (de Jong et al., 2019, 2022).

In human, alterations of NAc circuitry and connectivity have been implicated as definitive risk factors for pain chronification (Baliki et al., 2012; Apkarian et al., 2013; Hashmi et al., 2013; Vachon-Presseau et al., 2016a, 2016b).

Amygdala (Amyg)

Amyg is involved in pain-related emotion and defense behavior. Polymodal sensory information processed through the thalamus and cerebral cortex, inputs to the BLA (Veinante et al., 2013; Duvarci and Pare, 2014). BLA consists of Glu-ergic pyramidal neurons (80–85%) and GABA-ergic interneurons (15–20%) (Spampanato et al., 2011). From the BLA, Glu-ergic neurons project to the central nucleus of Amyg (CeA), which is the main output system of the Amyg. Pain information from the peripheral tissues via the spinal dorsal horn and PBN (external lateral division) terminates directly in the capsular region of the CeA (CeC). This PBN-CeC pathway transmits aversive signals important for threat and avoidance (Sato et al., 2015).

The CeA consists of its lateral and medial parts (CeL and CeM), in addition to the CeC, is occupied by GABA neurons expressing a variety of molecular markers, including somatostatin (SOM), protein kinase C-δ (PKC-δ), corticotropin-releasing hormone(CRH) neurotensin etc. (Duvarci and Pare, 2014; Kim et al., 2017; McCullough et al., 2018). PKC-δ $^{+}$ CeA neurons and SOM^{+} CeA neurons, two major subpopulations of CeA neurons, show distinct electrophysiological and morphologic properties (Adke et al., 2021) and opposing functions, i.e., the former is pro-nociceptive and occupies about 60% of CeA neurons, while the latter

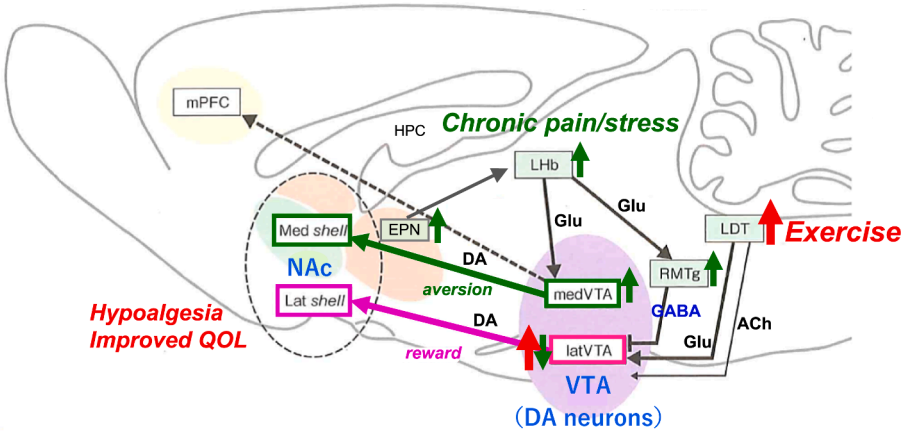

Fig. 2. Dual DA-ergic system in the VTA → NAc pathway The brain reward system consists of two systems, the lateral system, and the medial system, and in conditions of chronic pain and stress, the medial system is activated by the excitation of the lateral habenular nucleus (LHb), and the lateral system is suppressed via GABA neurons in the RMTg (green arrows). On the other hand, when exercising, LDT neurons are activated, so the DA neurons in the latVTA are activated and project to the lateral shell of NAc (red arrows). Thus, exercise activates the lateral system which promote reward behavior. This schematic model is based on Lammel et al., 2012. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is anti-nociceptive and occupies 40% (Wilson et al., 2019; Miller-Neilan et al., 2021; Chen et al., 2022). CeL/CeM neurons send robust projections to various brain regions, including forebrain, thalamus, hypothalamus, and brain stem (Liu et al., 2021; Singh et al., 2022) (Fig. 3). By projecting to the hypothalamus and PAG, they cause freezing, autonomic reactions responding to fear, stress, and pain (LeDoux et al., 1988; Johansen et al., 2011). PKC-δ $^{+}$ CeL neurons were shown to project to the zone incerta (ZI) to augment pain-related behavior (Singh et al., 2022). SOM^{+} CeL neurons project to the vlPAG to initiate passive freezing behavior, while CRH^{+} neurons were shown to mediate conditioned flight, positive response (Yu et al., 2016; Fadok et al., 2017).

BLA neurons projecting to the CeA mediates momentary arrests, i.e., freezing (Botta et al., 2020). An inhibitory pathway from the CeA to the vlPAG produces freezing by disinhibition of vlPAG excitatory outputs to pre-motor targets in the medullary reticular formation (Tovote et al., 2016).

In addition to CeA, BLA neurons project to the mPFC, NAc, HPC, etc., but their functions differ depending on the projection destination. When BLA neurons projecting onto the CeA or NAc were stimulated optogenetically, the former showed aversive behavior and the latter showed reward behavior (Namburi et al., 2015). Furthermore, those projecting to the CeA are mainly located on the lateral part (latBA) of the basal amygdala (BA) and those projecting to the NAc are on its medial part (medBA).

The heterogeneity of BLA neurons has been studied in detail by Kim et al. (2016). They discovered one gene whose expression increases due to electric shock (negative stimulus) (Rspo2) and another gene whose expression increases by cohabiting with a female (positive stimulus) (Ppp1r1b), and revealed that BLA neurons have different projection regions; positive neurons expressing Ppp1r1b and located on the posterior part of it (BLAp) project to the NAc and infralimbic cortex (IL) and negative neurons expressing Rspo2 and located on the anterior part of it (BLAa) project to CeA and prelimbic cortex (PL) (Kim et al., 2016).

The highest density of GABA-ergic neurons is present in the so-called intercalated cell mass (ITC), which surround the deep amygdaloid nuclei (Millhouse, 1986; Pitkänen et al., 1997; Duvarci and Pare, 2014). The ITC is interposed between the BLA and CeA and receives excitatory input from the infralimbic cortex (IL) and BLA (Neugebauer, 2015; Thompson and Neugebauer, 2017), and sends GABA-ergic projections to CeA projection neurons and control amygdala output via feedforward inhibition. The selective lesioning of ITC cells results in a marked deficit in extinction retrieval (Likhtik et al., 2008), suggesting that they play a central role in extinction of pain-related fear memory (See the section of "The role of IL in fear extinction").

The structure and functions of the Amyg are summarized in Fig. 3.

Medial prefrontal cortex (mPFC)

Divisions of mPFC and differential roles of PL/IL

The prefrontal cortex (PFC) consists of the mPFC, orbitofrontal cortex, ventrolateral PFC (vlPFC), and dorsolateral PFC (dlPFC). Here, we focus on the mPFC, which has a strong connection with limbic system such as Amyg, NAc and HPC.

The mPFC is further divided into dorsomedial PFC (dmPFC)/ventromedial PFC (vmPFC) in humans and prelimbic (PL)/infralimbic (IL) in rodents. The mPFC consists of 80–90% of Glu-ergic neurons and 10–20% of GABA-ergic interneurons, with interneurons containing parvalbumin (PV) (~52%), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), and somatostatin (SOM) (McKlveen et al.,2015).

It is well known that activation of GABA neurons in the mPFC, either by Glu-ergic inputs from the BLA or selectively by optogenetics, exacerbate pain by inhibiting mPFC pyramidal neurons projecting to the NAc

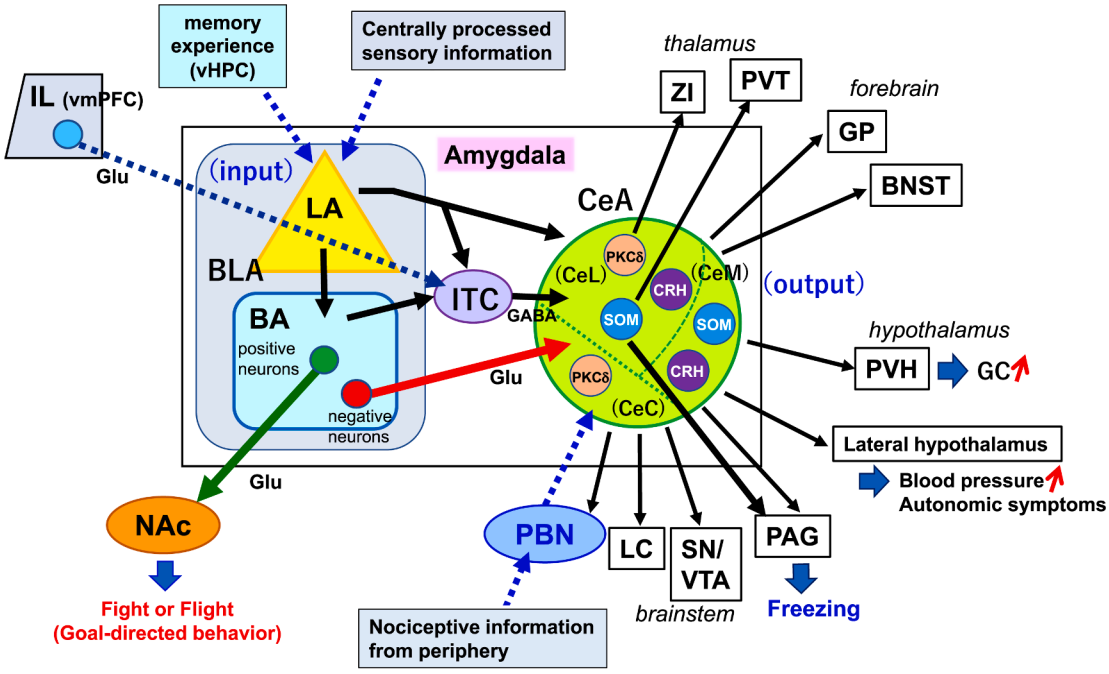

Fig. 3. Structure and function of the amygdala Pain information processed in the central nervous system mainly input to the basolateral nucleus (BLA), and pain information from the periphery directly input to the capsular region of the central nucleus (CeC) via the PBN. The central nucleus of amygdala (CeA) consists of GABA neurons with various genetic markers, such as protein kinase C-δ (PKC-δ). somatostatin (SOM), corticotropin-releasing hormone (CRH) etc. CeM and CeL neurons project to various brain regions, including thalamus, forebrain, hypothalamus, and brainstem. For example, SOM + CeL neurons project to the vlPAG and paraventricular nucleus of thalamus (PVT) and regulate fear expression (Penzo et al., 2014). Basal nucleus of amygdala (BA) consists of negative and positive neurons and sort the actions into negative "freezing" reactions, or positive (goal-directed) behaviors, the latter of which may have an advantage in the race for survival (LeDoux et al., 2017). Intercalated cell mass (ITC) receives excitatory input from the infralimbic cortex (IL) and project to the CeA. This schematic model is based on Johansen et al., 2011. Abbreviations; BNST, bed nucleus of stria terminalis; GP, globus pallidus; ITC, intercalated cell mass; LC, locus coeruleus; PBN, parabrachial nucleus; PVH, paraventricular nucleus of hypothalamus; PVT, paraventricular nucleus of thalamus; SN, substantia nigra; ZI, zona incerta.

(Lee et al., 2015) or to the PAG, a key midbrain structure involved in descending pain control (Cheriyan and Sheets, 2018). When BLA is over-excited by persistent pain, projection neurons in mPFC are suppressed via feed-forward inhibition, and the NAc and PAG are also suppressed, which may intensify pain (Ong et al., 2019).

In NPP model mice, cortico-PAG (C-P) neurons in layer 5 (L5) of PL, but not IL, showed a significant reduction in excitability (Cheriyan and Sheets, 2018, 2020). This infers that the functional roles of PL and IL in descending pain modulation are distinct.

Interaction between Amyg and PL/IL

BLA → mPFC projection. BLA inputs to the mPFC are involved in pain-related cognitive dysfunction and in fear conditioning (Klavir et al., 2017; Neugebauer, 2015; Thompson and Neugebauer, 2017), and preferentially target C-P projection neurons in layer 5 of the IL and cortico-amygdalar (C-A) projection neurons in layer 2/3 of the PL (Cheriyan et al., 2016). BLA projections to the mPFC synapse on layers 2–6 with a small percentage of these projections targeting PV-containing GABA-ergic interneurons (Gabbott et al., 2006). Thus, BLA projections can functionally modulate mPFC output via feed-forward inhibitory mechanisms (Giustino and Maren, 2015, 2017).

The relationship between BLA and PL/IL, which plays a central role in emotional learning through pain and fear, has been clarified in detail (Cheriyan et al., 2016) **(**Fig. 4**A).** The primary target of layer 5 (L5) neurons is the PAG. In IL, inputs from BLA preferentially terminate on C-P neurons, whereas in PL, BLA neurons primarily terminate on C-A neurons that project back to the BLA. It means that projection of BLA → IL is mainly involved in the descending pain inhibition than that of BLA → PL, and that the excitation of positive neurons of BLA (which project to the IL) acts on analgesia **(**Fig. 4**)**. Photo-stimulation of the BLA-PL projection increased freezing, while activation of BLA-IL neurons contributed to fear-extinction (Senn et al, 2014; Burgos-Robles et al., 2017).

PL/IL → Amyg projection. The distinct connections of PL/IL with Amyg nuclei are now clear; the PL-Amyg projection neurons predominantly target the BLA, whereas those of the IL project to the BLA and other Amyg divisions including the lateral amygdala (LA), ITC (Pinard et al., 2012), and possibly to the CeL. The projection to the ITC, directly or indirectly via BLA, is important in fear extinction (Duvarci and Pare, 2014; Giustino and Maren, 2015, 2017).

On the other hand, C-A neurons in the PL project back to the BLA. It has been demonstrated that 10–15% of BLA neurons are GABA-ergic (Spampanato et al., 2011). Since activity of BLA may be tightly regulated by these GABA interneurons, and a small dysregulation of GABA-ergic mechanisms in the BLA might result in hyperexcitation of BLA, which might lead to exacerbation of fear and pain (Prager et al., 2016), it will be of interest to know if these C-A neurons terminate on the interneurons or projection neurons in the BLA.

Pathway from mPFC to NAc

One of the primary prefrontal targets is the NAc (Brog et al., 1993; Ishikawa et al., 2008). It has been shown that IL projection neurons project onto the NAc to participate in reward behavior (Schwartz et al., 2017). In animals, when fear conditioning is formed with electric shock combined with pain predicted cues, the intake of rewarding sugar water decreases, but repeated sound stimuli extinct this fear conditioning and increase sugar water intake. In this situation, the pyramidal cells of IL are excited and the projection to NAc is increased. However, in NPP model animals (selective injury of sciatic nerve sensory branches), both IL activity and IL → NAc projection are decreased, and animals are unable to take reward actions against pain (Schwartz et al., 2017). Therefore, the suppression of reward behavior in chronic pain patients is thought to be partly due to a decrease in the projection of IL → NAc.

In humans, IL corresponds to vmPFC, and human brain imaging study shows that pain rating is suppressed by the activation of vmPFC (Eisenberger et al., 2011). If you look at a picture of your lover or partner, your pain rating for the same thermal stimulus will be lowered. At that time, the blood flow of vmPFC increases in the brain image, and the stronger the activation of vmPFC, the lower the pain rating. Activation of vmPFC-NAc pathway may have contributed to the lowered pain rating. Activation of vmPFC may also be involved in the extinction of fear responses, contributing to the feeling of "learned safety" (Eisenberger et al., 2011).

Exercise is a universal prescription for chronic pain states

Mechanisms of EIH

Recently, it has been clinically noted that exercise suppresses pain, and it has been reported that pain-related behavior is suppressed by loading exercise on model animals of NPP (exercise-induced hypoalgesia: EIH). The mechanisms of the analgesic effect of voluntary exercise (EIH) have been proposed, which involve changes at various

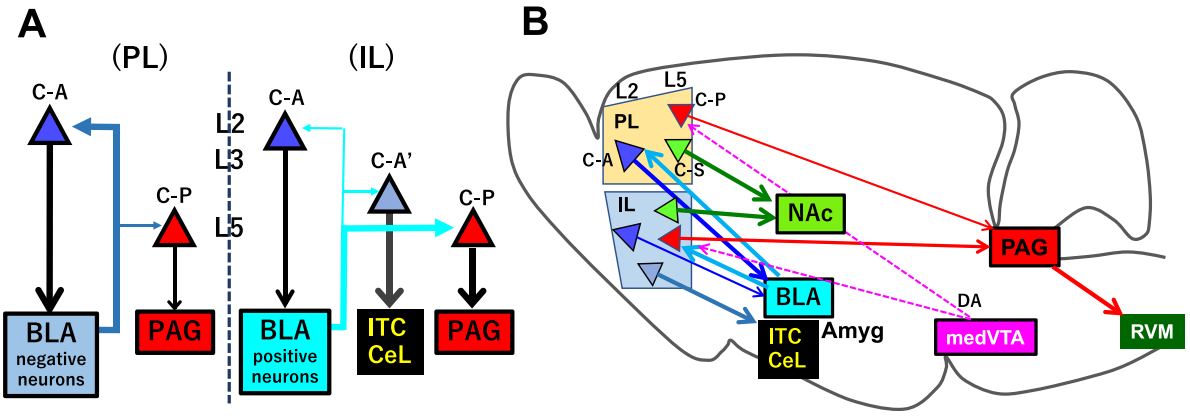

Fig. 4. Structure of the mPFC and interactions with subcortical structures A: The relationship between BLA inputs and PL/IL projection neurons. BLA inputs to the mPFC preferentially target cortico-PAG (C-P) projection neurons in layer 5 of the IL and cortico-amygdalar (C-A) projection neurons in layer 2/3 of the PL. Projection of BLA positive neurons to the IL is mainly involved in the descending pain inhibition, while those of BLA negative neurons to PL terminate on C-A projection neurons enhancing reciprocal connection (BLA-PL). This schematic model is based on Cheriyan et al., 2016. B: Projection neurons of mPFC project to the PAG (C-P neurons), the NAc (C-S neurons) and the BLA (C-A neurons). The former two projections are analgesic. C-A neurons may control the activity of BLA probably via GABA neurons in the BLA. medVTA DA neurons were shown to project to C-P neurons and contribute to the descending pain modulation (Huang et al., 2020).

levels of the nervous system, such as the descending pain modulatory system (Sluka et al., 2020) and the limbic system (for review, see Kami et al., 2017, 2022; Senba and Kami, 2017). We also reported that the function of GABA neurons in the dorsal horn of the spinal cord is maintained by exercise (Kami et al., 2016a; Senba and Kami, 2020). Epigenetic mechanisms are also driven in the spinal dorsal horn (Kami et al., 2016b). Moreover, it has been argued that myokines secreted from contracted muscles may play a role in EIH (Wang et al., 2022) and enhanced wound healing of injured skin by treadmill running may contribute to EIH (Kawanishi et al., 2022). In this review we focus on brain mechanisms, especially on the limbic system.

In animal studies using mice, we have shown that exercise 1) activates the brain-reward system (Senba and Kami, 2017; Kami et al., 2018), 2) enables goal-directed behavior by activating the Amyg → NAc pathway (Kami et al., 2020), and 3) suppress fear conditioning by inhibiting the vHPC → Amyg pathway (Minami et al., 2023). When a running wheel is equipped in a cage, a mouse will run on the running wheel voluntarily. The distance traveled is monitored by recording the number of revolutions. After a two-week acclimatization period, model mice of neuropathic pain underwent partial sciatic nerve ligation (PSL) surgery (Seltzer et al., 1990) and were allowed to do spontaneous exercise for further two weeks. As the mice recover after surgery, the mileage recovered to 70–80% of preoperative.On the other hand, the sedentary group of mice were kept in their cages with a locked running wheel by tape.

Exercise activates the NAc / brain reward system

When we examined the changes in pain behavior after PSL, the group that exercised (PSL-exercise) showed marked improvements in mechanical allodynia and thermal hyperalgesia compared to the group that did not run (PSL-sedentary). It also showed a positive correlation between total mileage and improvement of pain behavior at 2 weeks after PSL and found that mice that ran longer distance had a higher analgesic effect (Senba and Kami, 2017; Kami et al., 2018).

We looked at the brain reward system of such mice. DA-producing neurons in the VTA were immuno-stained with antibodies to the DA-producing enzyme Tyrosine hydroxylase (TH). We used the expression of nuclear protein FosB/ΔFosB in the nucleus as an indicator of neuronal activation.

DA neurons of the lateral VTA project exclusively into the lateral shell of the NAc, while medial ones to the medial shell of the NAc, and to the mPFC (Lammel et al., 2008, Lammel et al., 2012, Lammel et al., 2014) **(**Fig. 2**)**. We focused on the lateral VTA and found that activated DA neurons in the lateral VTA were increased in Naïve- or Sham (Sham-operated)-Runner groups. Although they were decreased after PSL surgery, the reduction was prevented significantly in PSL-Runner group mice. (Kami et al., 2018). Since P-CREB (phosphorylated cAMP response element- binding protein), a main transcription factor of TH-gene, immunoreactivity was expressed in these FosB/ΔFosB-positive, TH-positive neurons, the synthesis of DA seems to be increased in these neurons (Senba and Kami, 2017).

DA neurons in the lateral VTA may project to lateral shell of the NAc (Lammel et al., 2008, Lammel et al., 2012, Lammel et al., 2014). Then, what are the functions of the pathways from the medial VTA to the medial shell of the NAc, and mPFC? Chaudhury et al. (2013) used the length of social interaction and the amount of sugar water consumption as indicators of depression. Selective activation of the medial VTA-NAc pathway increased depressive symptoms and aversive behavior.

On the other hand, selective activation, or inhibition of the pathway projecting to the mPFC did not cause any behavioral changes (Chaudhury et al., 2013). However, recently, Huang et al. (2020) showed that dopaminergic projections from the VTA to mPFC modulate pain responses in a mouse model of neuropathic pain (spared nerve injury neuropathic pain model). DA enhances the activity of neurons projecting from mPFC layer 5 pyramidal neurons to the ventrolateral periaqueductal gray (vlPAG), culminating in analgesia. Thus, medial VTA → mPFC DA-nergic projection plays a role in descending pain modulation **(**Fig. 4 **B)**.

When animals do exercise, Glu and/or ACh neurons in the laterodorsal tegmental nucleus (LDT) are activated, which then activates DA neurons in the lateral VTA and neurons in the lateral shell of the NAc, i.e., the reward system (lateral system), leading to improved pain and quality of life (Kami et al., 2018). Moreover, Orexin neurons in the lateral hypothalamic area (LHA), which were shown to project to the VTA and activated by voluntary exercise, may contribute to the EIH (Kami et al., 2018). It has been demonstrated that the VTA is an important site of action for orexin's role in reward processing (Aston-Jones et al., 2010).

It has been demonstrated that exercise increases DA production in the VTA and activates the brain reward system (Greenwood et al., 2011). Moreover, when the DA neurons of the VTA were selectively suppressed, analgesia due to treadmill running was not observed in NPP model mice (Wakaizumi et al., 2016).

Exercise activates BLA → NAc pathway which enables goal-directed behavior

Glu-ergic pyramidal cells in the BLA are known to be overexcited due to fear of pain. They project to GABA-ergic interneurons in the mPFC and suppress pyramidal neurons projecting to the PAG and NAc, which surely contributes to the chronification of pain (Ji et al., 2010; Ji and Neugebauer, 2011; Lee et al., 2015).

Then, how can we regulate the excitability of BLA? We have found that voluntary exercise affects not only the VTA, but also the Amyg and NAc. Although the Amyg is closely related to pain, its relationship to the EIH has not been studied so far.

The basal amygdala (BA) consists of the medial (medBA) and lateral BA (latBA), We have already described that neurons in the latBA preferentially project to the CeA and those in the medBA preferentially project to the NAc (See, the section of Amygdala). Therefore, we divided the BA into lateral and medial parts to examine the response of neurons to PSL and locomotor activity.

First, many neurons in the BA are Glu-ergic and immuno-stained positive for EAAC1 antibodies. When these neurons are activated by exercise, they express FosB/ΔFosB. In the Sham-Sedentary group, almost no activated Glu neurons were observed in the BA, but in the PSL-Sedentary group, higher numbers of activated Glu neurons were observed in the lateral part compared to the medial part. Conversely, in the PSL-Runner group higher numbers of activated Glu neurons were identified on the medial part compared to the lateral part. That is, neurons in the latBA are activated by PSL and those in the medBA. Glu-ergic neurons are activated predominantly by voluntary exercise **(**Fig. 5 **A)**. Then, we injected a trace amount of the retrograde tracer Retro Beads Red (RBR) into the NAc and compared the BA of the voluntarily exercised mice. Then, about 60% of RBR signals were observed in the medBA, and 70% of NAc lateral shell projecting activated Glu neurons were detected in the medBA and 30% of them were observed in the latBA (Kami et al., 2020) **(**Fig. 5 **A)**. From these findings, it is reasonable to assume that exercise preferentially activates "positive neurons" of medBA that project particularly onto the NAc (Kami et al., 2020).

That is, in the defensive response when we are faced with a crisis or threat, a goal-directed behavior such as "fight or flight" occurs by the activation of the BA → NAc pathway, while negative reactions, such as freezing in the face of crisis, occur due to the activation of the BA → CeA pathway (LeDoux et al., 2017; LeDoux & Daw, 2018). More specifically, activation of somatostatin-positive (SOM^+) neurons in the CeA initiates passive freezing behavior (Fadok et al., 2017) and it has been shown that learned avoidance behavior requires an intact BA-NAc Shell circuit (Ramirez et al., 2015).

Next, we examined changes in neurons in the CeA in response to PSL and voluntary exercise. First, the majority of CeA neurons were

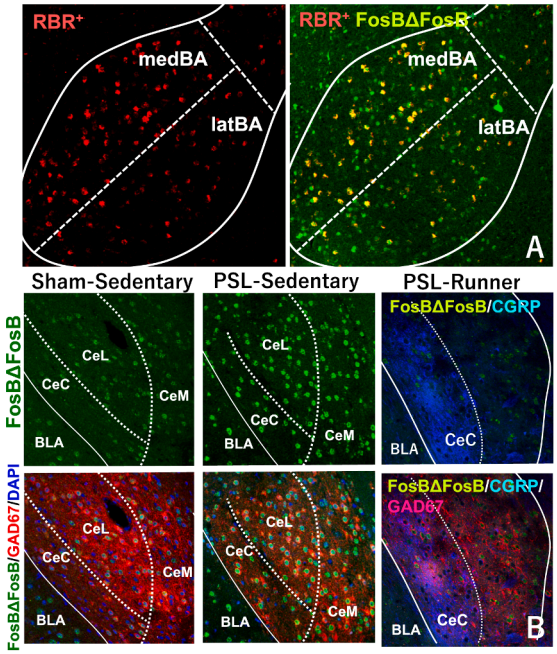

Fig. 5. Effects of exercise on BA neurons and CeA GABA neurons A: Neurons in the medial part of the basal amygdala (medBA) primarily project to the NAc, and neurons in the lateral part (latBA) mainly project to the CeA. When retrograde fluorescent tracer RBR was injected into the NAc, many of them were incorporated into medBA neurons, and these neurons expressed FosB in the nucleus by exercise. That is, exercise preferentially activates "positive" neurons in the medBA. B: Changes in CeA neurons in response to partial sciatic nerve ligation (PSL) and voluntary exercise were examined. The majority of CeA neurons are GABAergic, and almost all these neurons were activated by PSL, while the activation of these neurons was almost completely suppressed in the mice of PSL-Runner group (Kami et al., 2020). It should be noted that CGRP-immunoreactive fibers (blue) in the CeC are originated from CGRP neurons in the PBN. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

glutamate decarboxylase (GAD) -positive, i.e., GABA-ergic. We found that almost all these neurons were activated by PSL, but the activation of these neurons was almost completely abolished in the PSL-Runner group. That is, analgesia induced by exercise seems to reduce the input of pain information into the amygdala and attenuate the reactions of CeA neurons associated with pain (Kami et al., 2020) **(**Fig. 5 **B).** It is also possible that projection neurons in the IL activated by exercise (See section 4–4) may have projected to the ITC to activate GABA neurons projecting to the CeA to inhibit GABA neurons there (Kiritoshi and Neugebauer, 2018).

Then, what is "freezing"? Freezing is an evolutionarily conserved passive fear response. The idea that freezing is simply a negative reaction is disputed and suggested that it is a hold to the next action. More hopeless reactions that renounce everything are given the name "Quiescent immobility" (Kozlowska et al., 2015), which is a reaction to "deep or inescapable" pain or chronic injury, or injury by a predator, in animals. In humans, it occurs in response to severe visceral, skeletal muscle, or joint pain or to a stressful event. It is often prolonged beyond the period needed for physical healing and becomes maladaptive. Chronic pain such as complex regional pain syndrome type I may represent this type of immobility (Kozlowska et al., 2015).

On the other hand, LeDoux & Daw (2018) divided defensive responses into innate reactions and instrumental behaviors. These are all reactions mediated by sensory systems and Amyg, and the former appear as Freezing and/or Flight via PAG. The latter, instrumental behaviors, are further divided into goal-directed avoidance via NAc and habitual avoidance via dorsolateral striatum. If we take their argument into account, exercise will allow us to adopt goal-directed avoidance behavior rather than innate reaction in the face of a crisis.

Exercise activates pyramidal neurons in the mPFC

It has been demonstrated that 3 weeks of voluntary wheel running significantly increased c-Fos positive neurons in the PL in rats (Zlebnik et al., 2014) and 4 weeks of voluntary exercise increased FosB^{+} neurons in the mPFC in prairie voles (Watanasriyakul et al., 2019). We also examined the relationship between PL/IL neurons and EIH and found that non-GABA-ergic FosB^{+} neurons in the Pl and IL were increased by voluntary exercise (Kami and Senba, 2019). These neurons may be pyramidal neurons activated by disinhibition.

Exercise-induced changes in the brain revealed by our experimental study using mice are summarized in Fig. 6.

Fear conditioning and fear-avoidance thinking

Fear-avoidance thinking and chronification of pain

The "fear-avoidance model" that works on chronification of pain is well recognized (Lethem et al., 1983) **(**Fig. 7**).** When humans are injured and feel pain, they try to recover by confronting it and seek for therapy, but when they fall into catastrophic thoughts due to negative emotions and scary information, strong fear occurs, and they avoid movement which might cause pain. As a result, a vicious cycle of intense pain due to depression and physical dysfunction occurs, and the pain becomes chronic without being cured.

In this section, we will focus on the "fear" of pain, and examine the behavior born from the emotion of "fear" and fear conditioning, the brain mechanism that makes pain chronic. The central concept of the fear-avoidance model is fear of pain (Vlaeyen and Linton, 2000).

Mechanisms of fear conditioning

Contextual fear memory and ventral hippocampus (vHPC)

Phillips and LeDoux (1992) examined how the Amyg and hippocampus (HPC) that are affected by cues (such as sounds) and context (the background location) respectively, were involved in the formation of fear conditioning using rats. In rats whose Amyg were destroyed, sound and location could not be conditioned, while the destruction of the HPC, impaired only conditioning by location, so the HPC was shown to be involved in the formation of the context fear conditioning. Marschner et al. (2008) performed fMRI study in humans and reported that activation of the right Amyg was observed in cued conditioning, and activation of the left HPC was observed in the context conditioning.

The HPC is organized into dorsal and ventral subregions with distinct functions; the dorsal HPC is involved in cognitive functions such as conditioning and memory, and the vHPC is involved in emotional control (Strange et al., 2014; Vasic and Schmidt, 2017).

Functional difference of projections from BLA to NAc, CeA and vHPC

Fear and anxiety are emotional reactions that arise from feeling threatened. As to the difference between fear and anxiety, one popular distinction is that while fear occurs in response to a specific object, anxiety does not have a specific eliciting stimulus (Perusini and Fanselow, 2015). In normal conditions, fear or anxiety triggers a suitable avoidance response to protect oneself from threats. If the response is excessive or inappropriate, it is maladjusted. Anxiety disorders in humans are characterized by a response that overestimates the threat and tries to overdo it. Chronic pain can also be recognized as a kind of adjustment disorders.

BLA receives diverse sensory information and plays an important role in the formation of memories with positive and negative elements. The neural mechanisms that help identify them are preserved in many animal species, in which the BLA plays the central role. When Beyeler

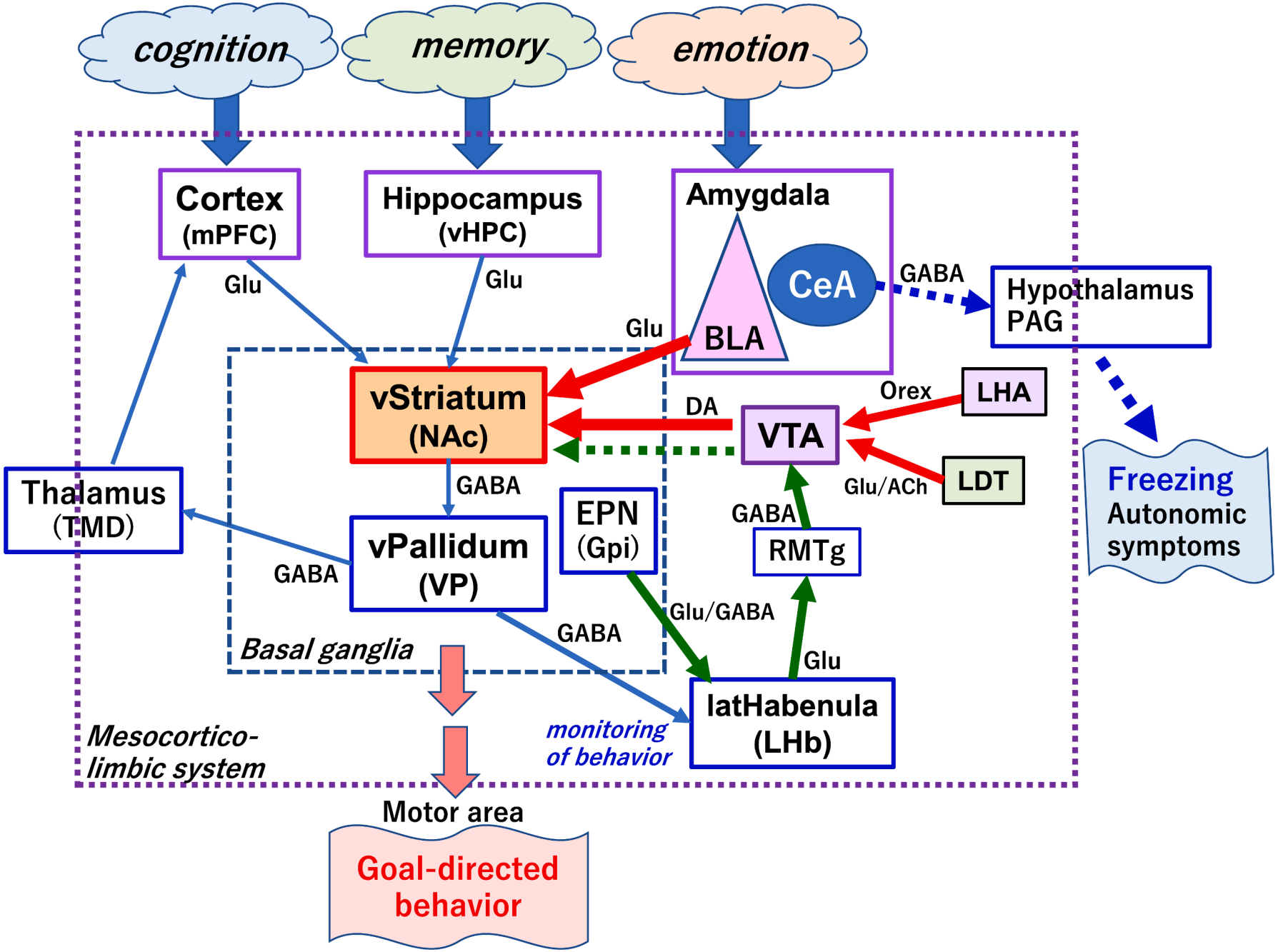

Fig. 6. Summary of exercise-induced changes in the mesocortico-limbic system (from experimental data in rodents) The NAc, an interface between the limbic and motor systems, links emotions to action. Whether the behavior is appropriate or not is monitored by the VP and LHb, and behavior correction is made via the brain reward system. In chronic pain states, EPN → LHb → RMTg pathway suppresses VTA DA neurons (green arrows). Exercise activates VTA DA neurons via activating LDT and orexin neurons in the lateral hypothalamic area (LHA), and positive neurons in the basal amygdala (BA) projecting to the NAc are also activated by exercise (red arrows), which enables goal-directed behavior. Negative response, like freezing, is inhibited by exercise, because CeA-GABA neurons are suppressed (blue dotted arrows). Note that a part of basal ganglia, such as ventral striatum (NAc), VP and EPN (GPi) are also involved in the mesocortico-limbic system. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 7. Fear-Avoidance Behavior and Pain Chronification When we are injured and suffer pain, we try to recover by confronting it, but when negative emotions and scary information lead to catastrophizing thoughts, strong fear occurs, and actions are avoided. As a result, a vicious cycle occurs in which pain intensifies due to depression and bodily dysfunction, and the pain becomes chronic without being cured. When a certain movement caused pain, we will be frozen and won't move again, which means that fear conditioning (fear memory) is formed. On the other hand, when we experience that it does not hurt even if we move, the fear memory is extinct, and we can face the problem at hand and recover. Exercise plays a part in this process by suppressing fear conditioning (Minami et al., 2023) and probably by promoting fear extinction. This schematic model is based on Lethem et al., 1983.

et al. (2018) examined the function of neurons projecting from BLA to NAc, CeA, and vHPC, respectively, they found that BLA → NAc neurons are more excited by the reward-containing cues, and BLA → CeA neurons are more excited by disgusted cues. BLA → vHPC neurons, on the other hand, cause behaviors due to anxiety.

Projections from vHPC to Amyg and mPFC

Conversely, regarding projection from vHPC, Ciocchi et al. (2015) showed that neurons of vHPC are classified by their projection destinations, mPFC, NAc, and Amyg, and anxiety-related behavior excited vHPC neurons projecting to mPFC. Reward-oriented actions primarily excited neurons projecting onto NAc and suppressed neurons projecting onto Amyg.

There are two types of vHPC pyramidal neurons projecting to the Amyg, one projecting to the BA and the other projecting to the CeA, and although the distribution region is the same, they do not overlap at all, and are functionally different (Xu et al., 2016) (Fig. 8). They showed that the vHPC → BA pathway works to form contextual fear memories, and the vHPC → CeA pathway works to reproduce fear memories.

The extinction of fear memories does not last forever. Four experimental phenomena have been widely regarded as demonstrating the resurgent reappearance of the fear responses: spontaneous recovery, rapid reacquisition, renewal, and reinstatement (Bouton, 2004; Monfils et al., 2009; Storsve et al., 2012).

When the communication between vHPC and mPFC is severed, the fear renewal that has been extinguished will not occur. Wang et al. (2016) revealed that the vHPC-PL pathway is involved in fear renewal as well as fear conditioning.

The role of IL in fear extinction

Extinction of fear memory is an important adaptation process for organisms to overcome threats from the environment, adapt to their environment and survive. It is well recognized that extinction is an active learning process that is obtained by repeated exposure to CS without harmful US and results in a reduction of conditioned fear responses (Kaplan and Moore, 2011).

The mPFC plays an important role in the extinction of fear due to the close communication between mPFC and Amyg. When the IL region is activated, the output from CeA is suppressed (Quirk et al., 2003), due to dense projections from IL to GABA neurons of ITC. Optogenetical activation of IL neurons during extinction training reduced fear expression and strengthened extinction memory (Do-Monte et al.,2015). From IL, there are Glu-ergic projections to BLA and NAc, and IL-BLA projection neurons were activated by the process of extinction of the fear response (Lingawi et al., 2019). But activation of IL-NAc projection neurons was not observed. Bloodgood et al.(2018) also found that inhibition of IL-BLA projection neurons by the DREADD technique impaired the extinction of fear responses.

Clinically, impaired extinction of fear memories has been the cause of mental illness stemming from various traumas and stress. In patients with posttraumatic stress disorder (PTSD), dysfunction of the brain regions involved in the extinction of fear conditioning, such as vmPFC, has been noted in a state of persistent fear response to events that caused the trauma (Marschner et al., 2008; Milad et al., 2009). Therefore, chronic pain has been proposed to be "persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury" (Apkarian et al., 2009).

The roles of vHPC, mPFC and Amyg in fear conditioning and extinction

Sierra-Mercado et al. (2011) have clarified that a triad of brain regions, including the mPFC, vHPC, and Amyg, form an essential brain circuit involved in fear conditioning and extinction. Within this circuit, the mPFC is thought to exert top-down control over subcortical structures to regulate appropriate behavioral responses (Giustino and Maren, 2015). Recently, it has been demonstrated that GPi (EPN) inactivation

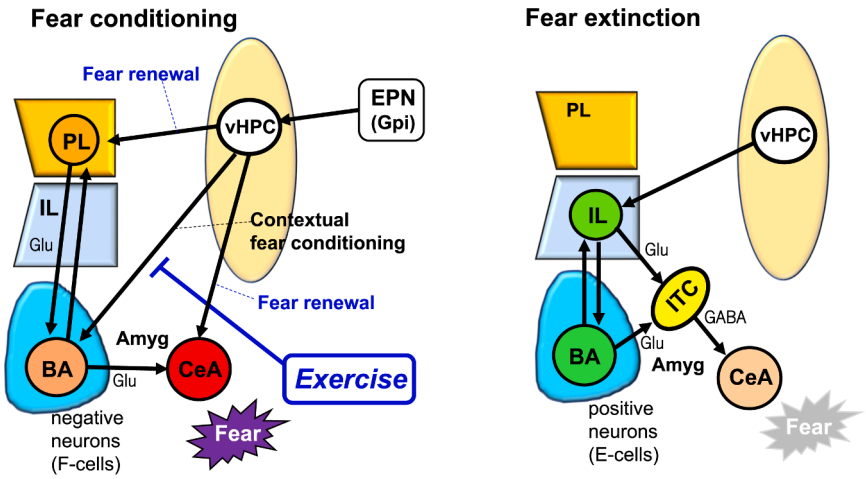

Fig. 8. Neural mechanisms of Fear conditioning and Fear extinction Fear conditioning and its extinction involve the vHPC, mPFC, and Amy. PL, BLA and vHPC are involved in the development of fear conditioning, and IL, BLA, and vHPC are involved in fear extinction (Sierra-Mercado et al., 2011). EPN → vHPC pathway also contributes to the acquisition of fear memory (Chen et al., 2020). Positive neurons of BA project to the IL and promote fear extinction (BA → IL → ITC → CeA pathway), on the other hand, reciprocal connection of BA negative neurons and PL enhance the activation of BA and strengthen the BA → CeA connection, promoting fear conditioning. Positive neurons and negative neurons may correspond to "fear cells (F-cells)" and "extinction cells (E-cells)" of Duvarci and Pare (2014), respectively. vHPC-BA connection promotes contextual fear conditioning and vHPC-CeA connection promotes fear renewal (Xu et al., 2016). Thus, a triad of mPFC, vHPC, and Amyg, form an essential brain circuit involved in fear conditioning and extinction. This schematic model is based on Sierra-Mercado et al., 2011.

impaired acquisition of fear memory and reduced freezing (Chen et al., 2020) **(**Fig. 8**)**. EPN, which is a member of basal ganglia, plays non-motor function by projecting to the vHPC, Amyg and LHb **(**Fig. 1**)**.

Neurons in the ITC receive CS information from the BLA, and send inhibitory projections to the CeA, the output system of the fear response, producing feed-forward inhibition to CeA neurons **(**Fig. 3**)**. It was found that reducing ITC neurons by the neurotoxin saporin impaired the extinction process of fear reactions (Likhtik et al., 2008) **(**Fig. 8**)**.

Fear memory extinction disorders in chronic pain state

In mouse models of neuropathic pain (NPP), spared nerve injury model, the extinction of contextual fear memories is impaired. These mice have been reported to have reduced neurogenesis in the DG of vHPC and impaired LTP formation between DG to CA3 (Mutso et al.,2012). Patients with chronic pain show anxiety, depression, and learning and memory impairment, which may be related to hippocampal atrophy and dysfunction. In patients with chronic low back pain or CRPS, a decrease in bilateral hippocampal volume has been noted (Mutso et al., 2012).

Exercise affects fear conditioning and extinction

Voluntary exercise has been shown in many studies to improve hippocampal function. Greenwood et al. (2009) therefore examined the effects of voluntary exercise on HPC-dependent conditioning, i.e., contextual fear conditioning. When rats were subjected to voluntary exercise for 6 weeks prior to fear conditioning, contextual fear memory was improved and fear response was enhanced, but extinction conditioning or extinction memory was not affected. In these rats, BDNF mRNA was increased in the dentate gyrus (DG), CA1 in the HPC and BLA (Greenwood et al., 2009).

On the other hand, in fear extinction conditioning, the question of whether an acute exercise bout, in the absence of a history of exercise, occurring in close temporal proximity to fear extinction can augment extinction was first addressed by Siette et al. (2014) and Mika et al. (2015), who reported that exercise only during and just after the acquisition of fear extinction learning improves fear extinction memory recall and reduces fear relapse. Bouchet et al., (2017) also found that 2 h of voluntary exercise attenuated contextual fear responses after 1 week and suppressed fear renewal, indicating that even in patients without exercise habits, short-term voluntary exercise may enhance extinction conditioning and increase the effectiveness of exposure therapy. This effect was pronounced in male rats (Bouchet et al., 2017).

These results show that a single bout of running can enhance fear extinction.

Recently, we have revealed that exercise suppressed vHPC-Amyg pathway by activating PV-containing GABA interneurons, i.e., via feed-forward inhibition (Minami et al., 2023), which might have prevented the formation of contextual fear conditioning. If IL pyramidal neurons are activated by voluntary exercise (See the section of "Exercise activates pyramidal neurons in the mPFC"), activation of the IL-BA-ITC pathway and/or IL-ITC pathway (Likhtik et al., 2008; Sierra-Mercado et al., 2011) may also contribute to the exercise-induced extinction of fear memory.

IL, or vmPFC in human, plays an important role in extinction learning (Sierra-Mercado et al., 2011), pyramidal neurons of which are activated by exercise and positive emotions. BLA's "positive" neurons also project to IL/vmPFC (Kim et al, 2016) to create a sense of learned safety and work to extinguish fear memories.

First-line treatment of chronic pain

Aiming to break out from fear-avoidance thinking

What can be said from the above is that: in patients with chronic pain, the limbic system, including the Amyg, HPC, mPFC, and the reward system, is dysfunctional, the fear response to pain is enhanced, and the extinction of fear memories is also impaired, which makes it difficult for chronic pain patients to get out of "fear-avoidance thinking". We propose that the key to getting out is to take advantage of the amygdala BA's behavioral sorting function (Kami et al., 2020, 2022), as we found that exercise activates BA → NAc neurons.

It is now clear that prolonged avoidance and physical inactivity exacerbate pain and have detrimental effects on our physical fitness and QOL. BLA → CeA neurons are more excited by aversive cues, while BLA → NAc neurons are more excited by rewarding cues (Namburi et al., 2015; Beyeler et al., 2016). If we only respond to disgusted cues in our environment, negative neurons will be activated and we can only take negative behavior, like freezing or immobility, but by finding cues that contain even a little reward that we can enjoy our life and get positive emotion, BLA → NAc neurons will be activated, and then we can take positive action like "goal-directed behavior" and fight against what threaten our healthy pain-free life. The opponent we fight against is our past inactive lifestyle. It means making exercise a habit and acquiring an active lifestyle. It is the "royal road" that leads to overcoming chronic pain by breaking out from fear-avoidance thinking.

We have recently demonstrated that 3 weeks of exercise therapy could change the functional connectivity in the mesocortico-limbic system and such alterations were related to improved motor activity of fibromyalgia patients (Kan et al., 2023 in this special issue).

Patients-oriented treatment of chronic pain

Cognitive reappraisal and fear extinction represent two different approaches to emotion regulation, which is critical for the treatment of chronic pain patients. If positive reappraisal (interpreting one's situation in a positive way) is successful and negative emotions are suppressed, brain imaging shows an increase of blood flow in the vlPFC and NAc, and a decrease of blood flow in the Amyg (Wager et al., 2008). Cognitive reappraisal activated lateral temporal cortex and modulated bilateral Amyg (Buhle et al., 2014). On the contrary, negative appraisal of internal and external stimuli may arouse negative emotion, which exacerbates pain state (Vlaeyen and Linton, 2000). It is thought-provoking that simply changing one's interpretation of one's situation can affect the brain function and change the way one feels in pain. CBT also acts on these brain regions to cause behavioral transformation and emotional changes (Seminowicz et al., 2013; Bao et al., 2022). Down-regulation of emotions is accompanied by effective connectivity alterations between the Amyg and prefrontal cortical regions (dlPFC, vlPFC and dmPFC) (Picó-Pérez et al., 2019; Berboth & Morawetz, 2021).

These are thought to be brain mechanisms that work effectively in "patient oriented medical care" such as exercise therapy, CBT, mindful acceptance, and combination of them. Clinical trials of multidisciplinary pain rehabilitation have been increasing tremendously recently and their effectiveness has been demonstrated in patients suffering fibromyalgia and musculoskeletal pain (Serrat et al., 2020; Llàdser et al., 2022; Liechti et al., 2023). These concepts are summarized in Fig. 9.

Prescriptions for the exercise therapy

The brain works as multiple networks

Finally, we will consider the pacing and adherence of exercise therapy from the aspect of the function of the brain working as networks. Recent advances in systems neuroscience have revealed important networks in the resting or active brain (Menon, 2011), such as the central executive network (CEN) (Smith and Jonides, 1999) including the dlPFC and the posterior parietal lobe (PPC), which is activated when performing cognitive tasks and plays an important role in working memory and for judgment and decision-making in goal-directed actions, and the default mode network (DMN), (Raichle et al., 2001), which is dynamically suppressed during tasks that require recognition, to make it possible to carry out accurate actions. The core areas of the DMN are

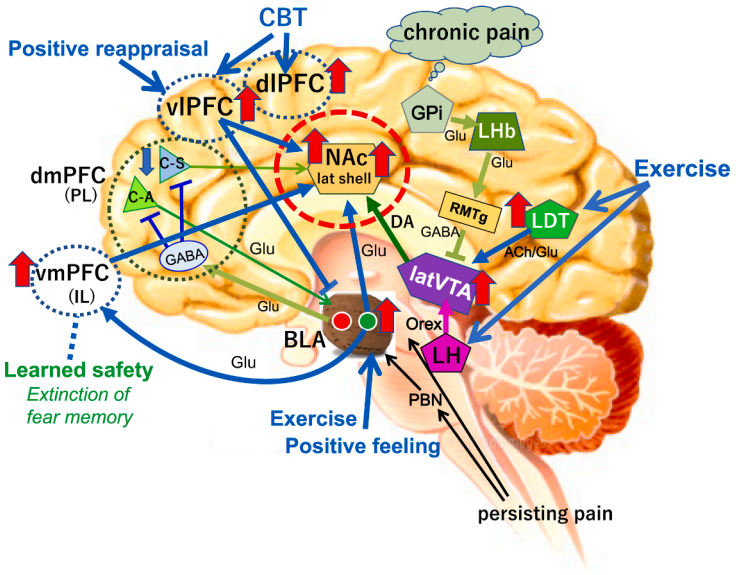

Fig. 9. Therapeutic interventions targeting the mesocortico-limbic system Even if we suffer chronic pain, it shows how exercise and/or positive emotions (e.g., immersing oneself in what one likes) and CBT (knowing the habits of one's way of thinking and changing one's behavior towards positive direction) activate the mesocortico-limbic system including the NAc, VTA, Amyg, mPFC etc. and suppresses pain behavior and depression. Successful "positive reappraisal" also targets vlPFC, NAc and Amyg (Wager et al., 2008). All these interventions are called "patient-oriented medicine" which promotes patients to change their lifestyle and way of thinking.

vmPFC and posterior cingulate cortex (PCC)/precuneus (PreCn).

The insula (INS) is highly sensitive to prominent (salient) events or stimuli, such as pain. In particular, the anterior insula (aINS) serves as an important hub for dynamic interaction with other large brain networks. Seeley et al. (2007) defined the "salience network (SN)" in which aINS and ACC work as the core component. Responding to various stimuli, the right aINS plays a decisive role in switching the other two major networks, i.e., activating CEN and inactivating DMN (Sridharan et al. 2008; Menon and Uddin, 2010).

A number of network alterations have been detected in various chronic pain patients. Key findings have been reported for the DMN (Baliki et al., 2014; Kucyi et al., 2014; Alshelh et al., 2017; Fallon et al., 2016; Iwatsuki et al., 2021). Chronic widespread pain patients showed decreased connectivity in the DMN and increased connectivity in the SN (van Ettinger-Veenstra et al., 2019; Hays Weeks et al., 2022). Exercise challenge has been shown to alter DMN dynamics in patients suffering chronic pain and fatigue (Rayhan et al., 2019; Li et al., 2022).

Prescription for exercise therapy based on the function of the brain networks

The brain network that is activated when you are not doing any task is the DMN, which is the state of the brain when you are dimly or ramblingly thinking. At times like these, original ideas come to mind. When some noticeable (salient) stimulus enters, the salience network is activated and the brain switches to work mode, and the DMN is suppressed. If you're too much absorbed in an assignment and so busy with work, the DMN won't work, and you may feel like you've lost your mind and yourself. However, once you become proficient in the task, both networks become cooperative and balanced. To improve QOL, it is important to balance both networks (Fig. 10). In patients with chronic pain, DMN function is thought to be weakened because the mind is trapped in pain as stated above. Therefore, in order to improve the QOL of patients with chronic pain, it is important to acquire lifestyle habits that activate DMN, suppress SN, and balance DMN and CEN (Fig. 10).

There are various kinds of exercise and walking in the natural environment enjoying the change of the seasons may activate the DMN

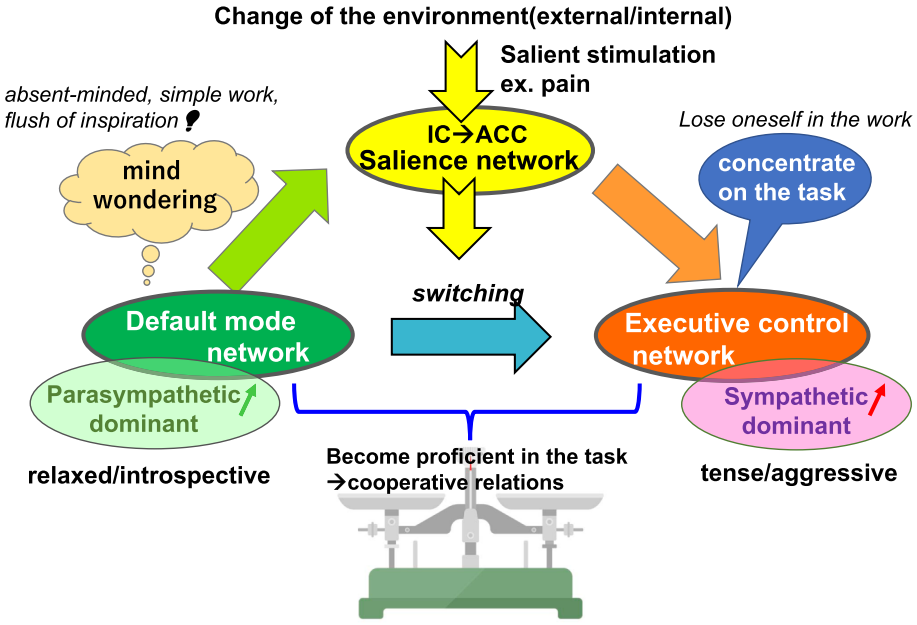

Fig. 10. The brain networks and their involvement in exercise habits in daily life When we are not doing any task, the default mode network (DMN) is activated. Our mind is free and relaxed, so original ideas might come to mind. When some salient stimulus such as pain enters, the salience network (SN) is activated and the brain switches to work mode (ECN). If we are too busy with work, we may feel like we've lost ourselves. It is essential to balance both networks to improve QOL. If we do exercise, pacing of exercise should be considered. Prescriptions based on the function of brain networks is essential for effective exercise therapy.

and mPFC. From this perspective, it is noteworthy that Amyg activation during a fearful faces task and a social stress task decreases after the walking in nature, whereas it remains stable after the walk in an urban environment (Sudimac and Kühn, 2022). Women seem to profit more from this salutogenic effects of nature (Sudimac et al., 2022).

The "pacing" of exercise by yourself is important. If you think that the more you do it, the more effective it is, you will do too much exercise, it may become biased toward a task-seeking CEN, and the pain may be enhanced due to stress and activated sympathetic function (Fig. 10).

Even if you start exercise therapy as a challenge and continue it every day or even 2–3 times a week, it becomes established as a lifestyle and a habit, and you will be able to move your body without thinking (Tricomi et al., 2009; Balleine and O'Doherty, 2010; LeDoux et al., 2017). This is the state in which the "adherence" of the exercise is established, and the CEN and DMN are coordinated in a well-balanced manner. Therefore, it is necessary to create a new exercise prescription with awareness of the brain networks in the future.

At first, it is important to maintain the motivation to continue exercising, but if you continue to exercise, it will become a habit and you will continue without being too conscious of it. This habituation involves the dorsolateral striatum (DLS), instead of NAc, as a neural circuit (Tricomi et al., 2009; Balleine and O'Doherty, 2010; LeDoux et al., 2017). It is similar to the fact that rehabilitation of motor function recovery activates the NAc to maintain motivation in the early stages, but if rehabilitation becomes a habit after several weeks or months, activation of the NAc is no longer necessary (Isa, 2017). Furthermore, when you lose control from the mPFC, the exercise therapy loses the goal and becomes compulsive (Burguière et al., 2015; Lüscher et al., 2020). To prevent this, it is necessary that mPFC is constantly activated, and cognitive therapeutic approaches will play a role.

Conclusion

So far, we have discussed the neuroscientific evidence how exercise activates the brain reward system/limbic system and reached a conclusion that exercise habits are essential for the prevention and treatment of chronic pain. In this review article, the authors took on a difficult task of integrating the daily-updated findings of neuroscience to provide a scientific basis for practical use in everyday pain clinic and pain rehabilitation situations. We hope that this objective has been achieved. We hope that patients with chronic pain will be able to overcome their chronic pain states by understanding the causes and processes of pain chronification, break free from fear-avoidance thinking, and proactively work to improve their daily lives, rather than just cringing in the face of the wall of chronic pain.

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CRediT authorship contribution statement

Emiko Senba: Conceptualization, Writing – original draft, Writing – review & editing, Visualization. **Katsuya Kami:** Data curation, Investigation, Methodology, Formal analysis, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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